contacting the protein with a cyclic saccharide cycloamylose having a degree of polymerization of 25 to 150, to produce a folded protein. See Claim 39.

The present invention also relates to a method of refolding a denatured protein, comprising:

contacting a polyoxyethylenic detergent with a denatured protein, followed by

contacting the protein with a cyclic saccharide cycloamylose having a degree of polymerization of 25 to 50 or 40 to 150, to produce a folded protein. See Claim 46.

The rejection of the claims under 35 U.S.C. §102(b) over Daugherty et al. taken with Takaha et al. is respectfully traversed. These references fail to disclose the claimed kits or methods.

As recited in the claims, the cyclic saccharide cycloamylose has a polymerization degree of from 25 to 150. As discussed in the present specification, the cyclic saccharide cycloamylose recited in the claims is distinct from β-cyclodextrin described in the reference. β-cyclodextrin, in contrast to the cyclic saccharide cycloamylose recited in the pending claims, has a degree of polymerization of 6 to 8. See page 2, last two lines to the middle of page 3, of the present specification.

As discussed at page 5, first full paragraph of the present application, the present invention is based on the discovery that the larger cyclic saccharide cycloamylose recited in the pending claims overcomes problems associated with β-cyclodextrin. As described in the specification at page 3, the β-cyclodextrin used by Daugherty et al. has problems associated with stability, and is not completely satisfactory (see the bottom of page 3 of the specification). In addition, Figures 1 and 2 of the present application clearly demonstrate that it takes a significant amount of time to refold an enzyme into its active form using β-cyclodextrin.

In contrast, the a cyclic saccharide cycloamylose having a degree of polymerization of 25 to 150 used in the present invention overcomes the difficulties associated with β-cyclodextrin. The Examples of the present application explicitly demonstrate this point.

In the Examples, citrate synthase (CS) denatured with guanidine hydrochloride was refolded with a variety of artificial chaperones. The results are presented in Table 1 at page 18 of the present specification. As stated at page 19, first full paragraph, using the claimed chaperon, the enzyme was refolded into the native form within as short as 2 hours. In contrast, as explained in the second full paragraph at page 19, with β-cyclodextrin, only about 30 to 40% of the enzymatic activity was recovered in 2 hours, and it took more than an overnight incubation to recover 100% of the enzymatic activity.

Takaha et al. describe producing cycloamylose with potato D-enzyme (see the Abstract). Nothing in this reference suggests using the a cyclic saccharide cycloamylose having a polymerization degree of from 25-150 in combination with the specified detergents for refolding proteins. Rather, this reference describes the physical characterization of the cycloamylose product of the potato D-enzyme described therein. Thus, this reference contains no teaching or description of protein refolding whatsoever.

In order for the claimed kits and methods to be obvious, the cited references must suggest the same.

Takaha et al. describe the physical characterization of the cycloamylose product of the potato D-enzyme described therein and does even mention using the cycloamylose for protein refolding. Therefore, one would not be motivated from Takaha et al. to substitute the β-cyclodextrin used by Daugherty et al. with the cycloamylose described by Takaha et al. First, Takaha et al. fail to even mention using the cycloamylose described therein for refolding. So, why would one skilled in the art even have reasonable expectation that the

cycloamylose described by Takaha et al. would even work for protein refolding. Second, Daugherty et al. explicitly teaches using β-cyclodextrin for protein refolding, and does not describe any disadvantages with this material. As such, one skilled in the art would not be motivated to substitute a a cyclic saccharide cycloamylose having a polymerization degree of from 25-150 as claimed for the β-cyclodextrin described by Daugherty et al.

In addition, one skilled in the art with Daugherty et al. and Takaha et al. would not have predicted the striking experiemental results presented in the specification described above. One with these references in hand would not have known that the claimed cycloamylose would have been so much more effective for refolding proteins as compared to β-cyclodextrin as convincingly demonstrated by the Examples of the present application. These striking results convincingly demonstrate that the claimed kit and methods are not obvious over Daugherty et al. and Takaha et al.

Based on the foregoing, the combination of Daugherty et al. and Takaha et al. fails to suggest the claimed kits and methods. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendments submitted above. The claims have amended for clarity in accordance with the Examiner's helpful comments and suggestions. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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Amendment Filed on:
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IN THE CLAIMS

--Claims 9-30 (Cancelled).

Claims 31-52 (New).--